Chapter

Immune Alteration Caused by Fibrous and Particulate Environmental Substances

Naoko Kumagai-Takei, Suni Lee, Kei Yoshitome, Nagisa Sada, Yasumitsu Nishimura and Takemi Otsuki

Abstract

Fibrous and particulate environmental substances such as asbestos fibers and silica particles cause not only lung fibrosis but also various health disturbances. Asbestos induce malignant tumors such as pleural mesothelioma and lung cancer. Silicosis patients exposed to silica particles show complications of various autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, and antineutrophil cytoplasmic antibody (ANCA)-related vasculitis/nephritis. The causative alteration of immune cells exposed to these environmental substances may form baseline modification of human immune system not only localized pulmonary lesions, alteration of alveolar macrophages, and others but also general immune system and changes of function in effector, regulatory, and cytotoxic T cells and natural killer cells. In this review, both (localized and generalized) immune alterations caused by environmental fibrous and particulate substances are summarized and reported.

Keywords: immune alteration, silica, asbestos, immune cells, autoimmunity, antitumor immunity

1. Introduction

The typical lung disease caused by occupational and environmental substances is pneumoconiosis [1, 2]. The pneumoconiosis is defined as health impairment caused by inhalation of dusts and mainly involves the lung. The restrictive lung disease defined as lung fibrosis occurred. The two main typical pneumoconioses are silicosis (SIL) and asbestosis [1, 2].

SIL is induced by inhalation of silica particle, SiO_2. It is white and powder form substance and relatively light. Thus, these particles deposit to the middle to the upper lobes of the lung [3, 4]. The alveolar macrophages (AM) are responsible to recognize these particles as external danger signal [5, 6]. Then, inflammasome inside of AMs, as dendritic cells, begin to initial reaction to produce cytokines such as interleukin (IL)-1β. The fibroblasts are called in to these area and form collagen deposition. Radiologically, these depositions of collagens are recognized as small nodules [5–7]. Thereafter, these nodules sometimes grow up more than 1 cm diameter defined as large nodules. The pathological lesions then spread many pulmonary complications such as tuberculosis, tuberculous pleurisy, secondary pneumothorax,

secondary bronchitis, and secondary bronchiectasis. In addition, lung cancer is also considered as complication of SIL [1, 2, 7].

The other typical pneumoconiosis is asbestosis [8, 9]. The asbestos is fibrous substance. The asbestos fibers are classified as serpentine group and amphibole group [10, 11]. The former consists of only chrysotile, and the latter includes five fibers, i.e., amosite, crocidolite, tremolite, anthophyllite, and actinolite. The serpentine is curly and the amphibole group is needle-like. These fibers are fibrous, so they are relatively heavy. Thus, the deposition occurred in the middle to lower lung lobes. Then, as similar to silica particles, the inflammasome in AM is starting reactions to form fibrosis [5–7]. The difference of form of fibrosis depends on fibers' length. Asbestos fibers possess more than 3 aspect ratio, and thus it is relatively long [10, 11]. Then, the collagen deposition also forms irregular and kind of linear pathology, not like nodules caused by silica particulate substances. Radiologically it is defined as irregular shadows and sometimes develops to honeycomb shadow [8, 9]. Even though doses are not higher to cause asbestosis and lung fibrosis, other asbestoses causing complications are known. These are pleural plaque (PP), benign pleural effusion, rounded atelectasis, and diffuse pleural thickening [12, 13]. In addition, the important complications are malignant tumor such as lung cancers and malignant mesotheliomas (MM). In addition, the report from the International Agency for Research on Cancer (IARC) shows possibility of relation between asbestos exposure and laryngeal, gastrointestinal, ovarian, and bile-duct cancers [14, 15].

The SIL patients often complicate with autoimmune diseases [7, 16]. Caplan syndrome which is defined as complicated rheumatoid arthritis (RA) with coal miner pneumoconiosis is well known and classical. Additionally, various epidemiological studies indicated the complications of various autoimmune diseases such as systemic sclerosis (SSc), systemic lupus erythematosus (SLE), and, more recently, antineutrophil cytoplasmic antibody (ANCA)-related vasculitis/nephritis [7, 17]. To consider the mechanisms of causing dysregulation of immune tolerance in SIL patients, the exposure to silica particles may affect to the human immune cells to form bases.

Since asbestos fibers are different physiologically with silica particles, asbestos is fibrous, not particulate, but asbestos fibers are the mineral silicate. Thus, chemically, fibers consist of SiO_2 and other elements such as iron, magnesium, and sodium. The carcinogenic activity of asbestos is considered dependent on iron contents [14–18]. Therefore, crocidolite ($Na_2Fe^{2+}{}_3Fe^{3+}{}_2Si_8O_{22}(OH)_2$) is considered to possess the strongest carcinogenic activity, and amosite ($Fe_7Si_8O_{22}(OH)_2$) is assumed the next [14–18]. However, even though chrysotile ($Mg_3(Si_2O_5)(OH)_4$) does not contain iron, this serpentine fiber is also considered as a carcinogenic substance. Although the carcinogenic activity is lower than crocidolite and amosite, chrysotile also cause cancers by its physical form to induce AMs as frustrated (not being able to digest as foreign danger material and produce reactive oxygen species (ROS) as free radicals) and contamination of amphibole fibers as natural mineral products [14, 18, 19]. As mentioned above, silica particles are assumed to influence the human immune system [7, 17].

As shown in **Figure 1**, silica particles and asbestos fibers affect various immune cells such as CD4+ helper T (Th) cells (responder T cells: Tresp), Th17, regulatory T cells (Treg), CD8+ cytotoxic T lymphocyte (CTL), and natural killer (NK) cells. In this review, the effects of silica or asbestos on Tresp, Treg, and Th17 are compared and summarized from our findings as well as reported literatures. Thus, regarding effects of asbestos on CTL [20], briefly, the proliferation and differentiation using mixed lymphocyte reaction (MLR) assay were inhibited, as well as using in vitro activation assay with chrysotile fibers or analyses of peripheral blood CTL derived from patients with PP and MM. As a result, in CTLs from asbestos-exposed

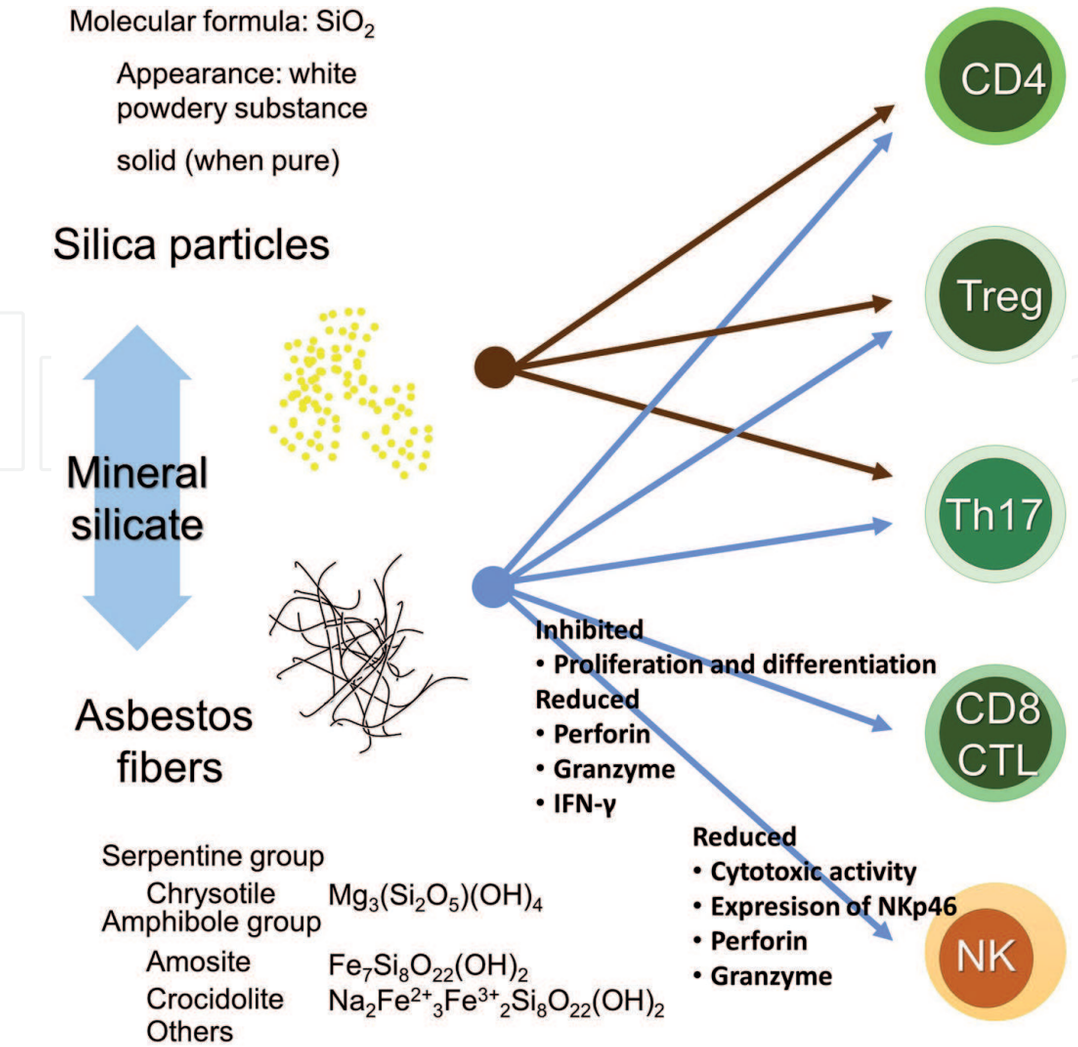

Figure 1.
The aim of this review is to present the effects of silica particles and asbestos fibers onto various human immune cells such as CD4+ T helper cell, regulatory T cell (Treg), Th17 cell, CD8+ cytotoxic T lymphocyte (CTL), and natural killer (NK) cell. Although physiological features of silica and asbestos are different, particulate and fibrous substances, chemically Si and O, are the core elements. For CTL, asbestos fibers inhibit its proliferation and differentiation as well as reduction of cytotoxic materials such as perforin, granzyme, and interferon (IFN)-γ. In addition, exposure to asbestos fibers on NK cell; its cytotoxic activity; expression of one of the activation receptors, NKp46; and production of cytotoxic molecules (perforin and granzyme) are reduced.

patients, especially in MM, cytotoxic molecules such as perforin, granzyme, and interferon (IFN)-γ were reduced. These results indicated that asbestos exposure causes reduction of antitumor immunity regarding CTL function [20–23].

In addition, in our analyses using NK cells derived from healthy volunteers (HV) and incubated with asbestos fibers, human NK cell line exposed to asbestos fibers continuously revealed some NK cell-activating receptors including NKG2D, NK2B4, and NKp46 and intracellular perforin and granzymes as shown in **Figure 1**. Particularly, the expression levels of NKp46 were correlated with NK cell killing activity against tumor cells. These results also indicated that asbestos exposure reduced antitumor immunity regarding NK cell function [24, 25].

2. Effects of silica particles and asbestos fibers on CD4+ Tresp

The effects of silica particles and asbestos fibers are shown in **Figure 2**.

Silica particles chronically activate Tresp cells. As a result, the expression of CD69, one of the earlier activating cell surface markers of Tresp, was gradually

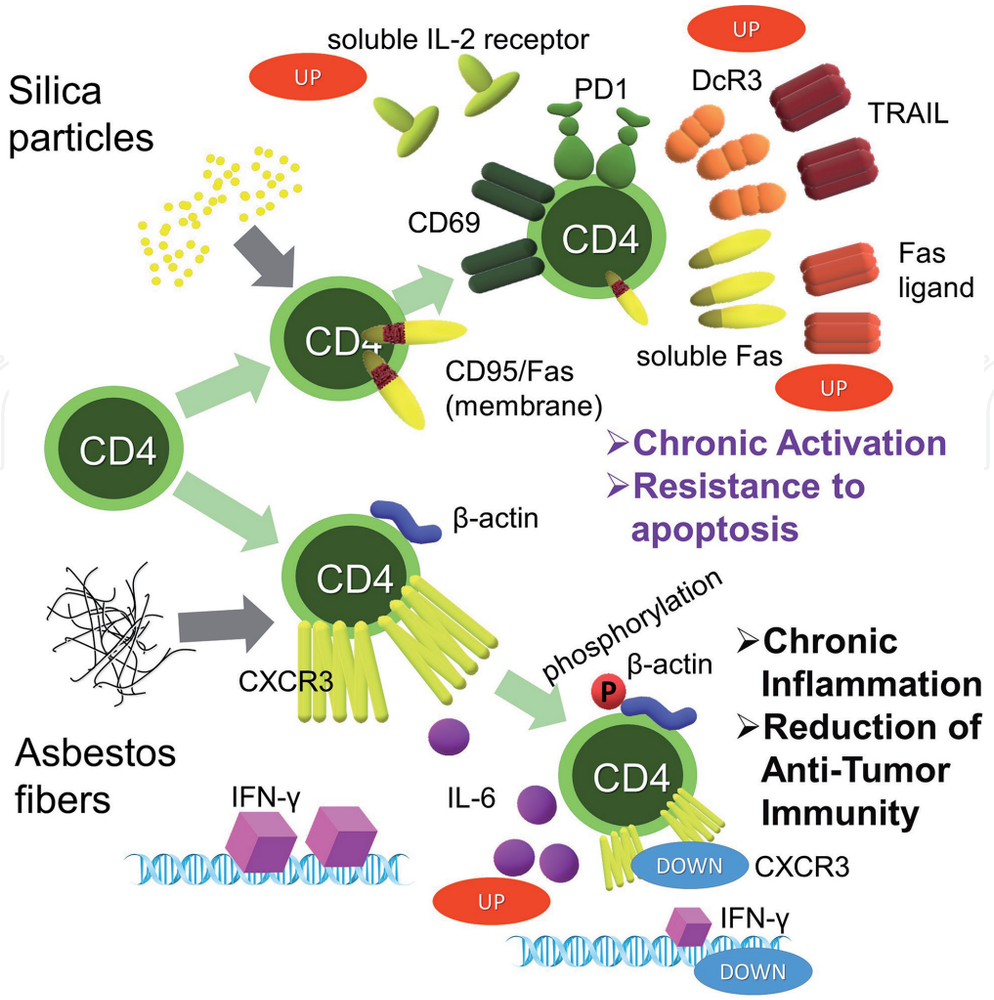

Figure 2.
The effects of silica and asbestos on CD4+ responder T cell. Silica caused chronic activation and resistance to Fas-mediated apoptosis. On the other hand, asbestos exposure causes chronic inflammation and reduction of antitumor immunity.

increased when peripheral blood mononuclear cells (PBMC) were incubated with silica in vitro [26]. In addition, the mRNA expression of program death-1 (PD-1) molecules as the activation marker of Tresp was compared between Tresp derived from HV and SIL patients. As a result, PD-1 was highly expressed in SIL than those in HV. Moreover, serum soluble IL-2 receptor (sIL-2R) concentration showed higher in SIL than HV [27]. The sIL-2R is considered as one of the markers which reveal chronic activation of Tresp, and various collagen diseases and autoimmune diseases are shown to be higher (not like T-cell tumors such as T-lineage malignant lymphoma and leukemias) than HV [28]. All of these results indicated that Tresp in SIL are chronically activated by silica exposure. It is assumed that circulating Tresp may repeat encounters with silica particles on lung fields and pulmonary lymph nodes [29].

On the other hand, serum from SIL showed higher soluble Fas (sFas) than these from HV [30]. The sFas is produced by alternative splicing of Fas, CD95, death receptor, and gene and binds with Fas ligand at the extracellular area. In addition, if sFas is alternatively spliced, transcription of original wild-type Fas is reduced. Thus, membrane Fas is decreased, and Fas ligands are consumed at the outer spaces [31]. Moreover, other spliced variants of Fas gene remained as binding site with Fas ligand and loose membrane-binding domain [32]. So, these may also act as sFas to prevent Fas ligand-induced apoptosis. In addition, similar scenario of sFas and Fas ligand is assumed in TNF-related apoptosis-inducing ligand (TRAIL) and its

receptor. Similar to sFas, cells sometimes produce decoy receptor to TRAIL, such as membrane-bound decoy receptor (DcR) 1 and 2 and soluble DcR3 [33, 34]. In this viewpoint, mRNA of DcR3 was highly expressed in SIL PBMCs compared with those from HV [35]. In addition, serum DcR3 levels were also higher in SIL rather than HVs (data unpublished).

Taken together, Tresp exposed chronically and repeatedly to silica particles reveal chronic activation and resistance to apoptosis. Thus, chronically activated Tresp, in which probably self-antigen recognizing Tresp are also included, survive longer. This makes the chance of encounter Tresp and self-antigens more frequent [29, 36].

Regarding asbestos fibers, a human T-lymphotropic virus (HTLV) 1 immortalized human polyclonal T lymphocyte cell line, MT-2 [37], was applied to explore the chronic effects of asbestos on human T cells. Although temporally and relatively high-dose exposure induced ROS production, activation of mitochondrial apoptotic pathway, and cell death [38], relatively low-dose and continuous exposure (more than 8 months) in vitro afforded the acquisition of resistance to asbestos-induced apoptosis [39]. These continuously exposed sublines (exposed to chrysotile or crocidolite) revealed C-X-C chemokine receptor type (CXCR) 3 expression [40]. This receptor is important to call tumor-attacking T cells into the tumor surrounding area. In addition, one of the important cytokines against tumor cells, IFN-γ expression, was also decreased compared with asbestos-unexposed original cell line. These findings were confirmed using Tresp derived from PP or MM patients [41]. In addition, when Tresp derived from HV and patients with PP or MM were stimulated in vitro, IL-6 was produced higher in the supernatant of Tresp derived from PP or MM rather than those from HV [41].

In these findings together with the abovementioned asbestos' effects on CTL and NK cells, continuous asbestos exposure induces reduction of antitumor immunity and increases chronic inflammation [42]. These are assumed to be the one of the backgrounds for occurring mesothelioma after long latency since initial exposure to asbestos fibers and rapid progress of malignant tumor once it occurred [42].

Additionally, continuously exposed sublines showed excess phosphorylation of β-actin (**Figure 2**) with over binding of some molecules in cytoskeletal component such as vimentin, α-tubulin, and myosin 9 [43]. These indicate that changes of cytoskeletal molecules after continuous exposure to asbestos fibers possess important roles for alteration of cellular and molecular functions [43], since asbestos fibers are not adsorbed into the cell inside due to the fibers' size and physical properties.

3. Effects of silica particles and asbestos fibers on Treg

Treg is defined as CD4+, CD25+, and forkhead box P3 (FoxP3) as transcription factor positive [44]. Treg inhibit the activation and proliferation of Tresp after antigen stimulation. Thus, decreases of volume and function of Treg cause excess reaction to antigen including self-antigen. This proceeds to allergy and autoimmune diseases. Contrary, increases of function and volume of Treg suppress Tresp activation and proliferation. Thus, considering the complications in silica- or asbestos-exposed patients, the former show autoimmune disorders and the later present with malignant tumors. Therefore, silica may cause decrease of Treg's function or volume. On the other hand, asbestos may enhance Treg's function or volume [44–46].

Initially, Treg's (CD4+ and CD25+ fraction in PBMC derived from SIL) suppressive function against alloantigen-stimulated Tresp (CD4+ and CD25−) proliferation was assayed using MLR. As a result, Treg fraction from SIL was less suppressive than

those from HV when added as one fourth to half of Tresp number [47]. Although this result indicated that silica exposure reduces the function of Treg, as mentioned above, Tresp in SIL were chronically activated to express CD25 on their cell surface as the activation. Thus, peripheral CD4+ and CD25+ fraction may include chronically activated Tresp. To confirm whether or not silica exposure reduces function of Treg or its volume, Fas expression in Treg (FoxP3+) between SIL and HV was compared, and those from SIL showed higher [27]. Thereafter, if PBMC from HV were cultured with silica particles in vitro, CD25-positive cells were increased in CD4+ cells, but FoxP3+ cells decreased [27]. The interpretation of this finding is that silica exposure induces chronic activation of Treg similar to Tresp. As a result, Treg express excess Fas and proceed to Fas-mediated apoptosis. Then, early loss of Treg occurred in the peripheral blood of SIL. Together with the abovementioned long survival and apoptosis resistance in Tresp from SIL, SIL showed an imbalance of Tresp and Treg (Tresp dominant), and this tendency is known in various autoimmune diseases (**Figure 3**). So, it can be considered that silica exposure yields the basic immune alteration which causes occurrence of autoimmune diseases [17, 48]. With some individual factors such as HLA types and other single-nucleotide polymorphisms (SNPs) in various genes related to immune function such as ILs or other growth factors such as TNF-α, SIL often complicates with autoimmune diseases.

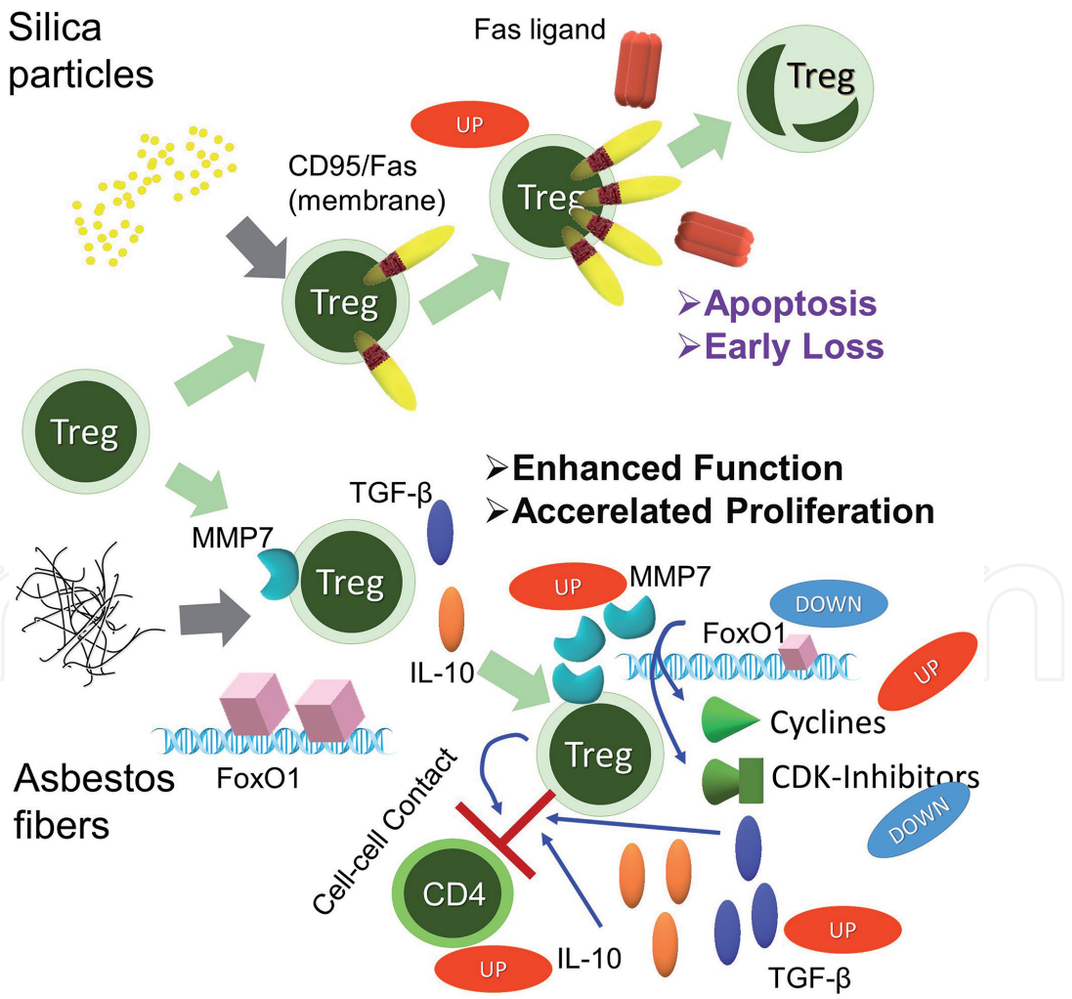

Figure 3.
The effects of silica and asbestos on Treg. Silica induces enhanced expression of death receptor, Fas, causing excess apoptosis and early loss of Treg. On the other hand, asbestos enhances Treg function via cell-cell contact and overproduction of soluble factors, IL-10 and TGF-β. In addition, asbestos-induced decreased expression of FocO1, transcription factor, causes acceleration of cell cycle progression by upregulation of cyclins and downregulation of CDK inhibitors. Taken together, asbestos induces enhancement of Treg quality and quantity causing reduction of antitumor immunity.

To investigate the effect of asbestos on Treg, the cell line, MT-2, which was used to continuous exposure model to asbestos, was reported to possess Treg-like function [49, 50]. Thus, the Treg function in original MT-2 cells which never meet with asbestos fibers and MT-2 subline continuously exposed to asbestos. As a result, inhibitory effects on Tresp proliferation were stronger in subline rather than original line by cell-cell contact assay. In addition, subline showed overproduction of IL-10 [39] and transforming growth factor (TGF)-β when compared with original line [51, 52]. Since these two cytokines are typical soluble factors for Treg suppressive function, knockdown clones for IL-10 or TGF-β were compared with their suppressive activity with subline using transmembrane assay (designing only soluble factors, but not cells, can slip through the membrane). As a result, Tresp proliferated much more with transmembrane cultured with knockdown clones for IL-10 or TGF-β than subline [51]. Thus, Treg function was enhanced by asbestos continuous exposure via cell-cell contact as well as excess production of soluble factors.

It was found that transcription factor, FoxO1, was reduced in asbestos' continuously exposed subline [53]. FoxO1 affects cell cycle regulator genes such as cyclins and cyclin-dependent kinase (CDK)-inhibitors (CDK-Is) such as ink4 family (p15, p16, p18, and p19) and cip/kip family ($p21^{cip1}$, $p27^{kip1}$, and $p57^{kip2}$). To compare the expression of cyclins and CDK-Is, cyclins were highly expressed, while CDK-Is were weakly expressed in subline compared with original cells. In addition, in cell cycle phase analysis, subline showed higher S/G1 ratio (S-phase% was divided with G1 phase%) than that of original line. In addition, knockdown of FoxO1 in subline using siRNA induced increased expression of cyclin D1, the most enhanced expression in subline [54]. These results indicated that reduced FoxO1 caused by asbestos exposure induced enhancement of cell cycle progression.

Taken together, asbestos exposure increases Treg function and volume (**Figure 3**).

In addition, it was found that matrix metalloproteinase (MMP)-7 gene expression was enhanced in asbestos-exposed subline rather than original line [55]. Although the role of this finding is not explored well, MMP-7 also known as matrilysin is considered as the enzyme related to the cancer metastasis and invasion to cut extracellular matrix such as proteoglycan, fibronectin, and collagen type IV [56]. In addition, MMP-7 affects apoptosis by cutting membrane-bound Fas ligand to proceed as soluble form. If Treg produce much more MMP-7 due to asbestos exposure, tumor-attacking Tresp may proceed to apoptosis. Although the detailed examinations should be done, this alteration may be important to consider asbestos exposure and tumor occurrence.

4. Effects of silica particles and asbestos fibers on Th17

Th17 cells are differentiated by cytokine balance surrounding T helper cells in balance with Treg. Th17 is promoted with IL-6 and TGF-β, whereas Treg is skewed only by TGF-β. Thus, this balance is important for both differentiations [57]. Th17 is considered to contribute to the occurrence of autoimmune diseases via cytokine production such as IL-17 and IL-22 [58]. Thus, it should be investigated how silica particles affect the function and volume of Th17 regarding complications of SIL. Unfortunately, there are no reports regarding this viewpoint. Future investigations are required to explore the role of silica particles on the function of TH17 and changes of volume.

On the other hand, there were couples of articles regarding Th17 and silica-induced lung fibrosis. Lo Re et al. reported that rapid lung recruitment of Th17

producing IL-17A was mediated by macrophage-derived IL-23 and was important to form inflammation, but not fibrosis, in experimental silicosis using animal model [59]. Then, Song et al. studied using mice model of silica-induced fibrosis and found Treg promotes Th17 differentiation via TGF-β1 and IL-1β [60]. Although they did not define inflammation and fibrosis in detail, there might be some role in Treg to activate Th17 for the development of lung fibrosis. Mills et al. found the importance of γδT cells with Th17 to produce IL-17 by analyzing details of inflammasome activation [61]. Thus, this study was not defined in silica-induced fibrosis. However, they considered the roles of Th17 and γδT cells for the development of many autoimmune and chronic inflammatory diseases. Thus, silica exposure may affect γδT cells, too. Chen et al. investigated that in the mouse model, neutralization of IL-17A delayed progression of silica-induced lung inflammation and fibrosis [62]. They assumed this was caused by decrease of IL-6 and IL-1β and increase of Treg. Song et al. from the same group showed the importance of IL-1β on lung fibrosis caused by silica using IL-1 type I receptor antagonist [63]. Then, their findings indicated that regulating IL-22 and IL-1β organizes Th1 and Treg differentiations, and then, these were important for promotion of lung inflammation caused by silica via Th17 promotion (**Figure 4**).

Interest reports to reveal importance of MyoD88 for lung fibrosis and inflammation caused by silica using MyD88 knockout mice were studied by Re et al. [64]. They found that accumulation of Treg and cytokines such as IL-10, TGF-β1, and platelet-derived growth factor (PDGF)-B contributed to lung inflammatory and granuloma responses, whereas this was not with Th17 influx. Furthermore, Dai et al. focused on the Wnt/β-catenin pathway for silica-induced fibrosis. They agreed with Th17 enhancement [65]. In addition, if they blocked Wnt/β-catenin pathway, Th1/Th2 polarization was delayed, and this delay was caused by Treg and Th2 response. Then, they suggested that Wnt/β-catenin pathway regulates Treg and contributes to fibrogenesis in silicosis. Additionally, other than Th17, Liu et al. reported the role of IL-10-producing regulatory B cell in silicosis, since this B cell increased in silica instillation in mouse model [66]. The produced IL-10 seemed to suppress Th1 response with IL-10 produced from Treg.

Back to Th17, Li et al. studied alteration of expression in 4-1BB (CD137, TNFRSF9) which is an inducible costimulatory receptor expressed on activated T cells, during lung injury caused by silica using animal model [67]. Then, inhibitor for 4-1BB revealed reduction of Th1 and Th17 responses measured by TNF-α, IFN-γ, and I-17A production. Thus, 4-1BB pathway is also involved in Th17 cells toward inducible lung fibrosis due to silica exposure.

Taken together, Th17 is assuming to possess an important role in silica-induced lung fibrosis via other immune cells such as Treg and γδT cells as well as various cytokines and signaling molecules.

How about the role of Th17 in asbestos-exposed pathology? Ferro et al. reported that amphibole, but not chrysotile, induced antinuclear autoantibodies (ANA) and IL-17 in mice model [68]. In this study, they also found that there was a significant increase of suppressor B cells defined by CD19+, CD5+, and CD1d+ in the lung as well as the spleen. They considered amphibole and serpentine groups can induce inflammatory change; however, only amphibole is able to yield an autoimmune response. In addition, their studies were extended to assess erionite, which is naturally occurring fibrous mineral and belongs to a group of minerals called zeolites, not asbestos [69]. Physically, this is resembling to amphibole. In addition, this fiber is known to be a human carcinogen. The prevalence of malignant pleural and peritoneal mesothelioma due to erionite exposure in the Cappadocia region of Central Anatolia, Turkey, is very high. Zebedeo et al. reported that exposure of erionite as well as amphibole asbestos on bone-marrow-derived macrophage caused increasing ANA positive prevalence

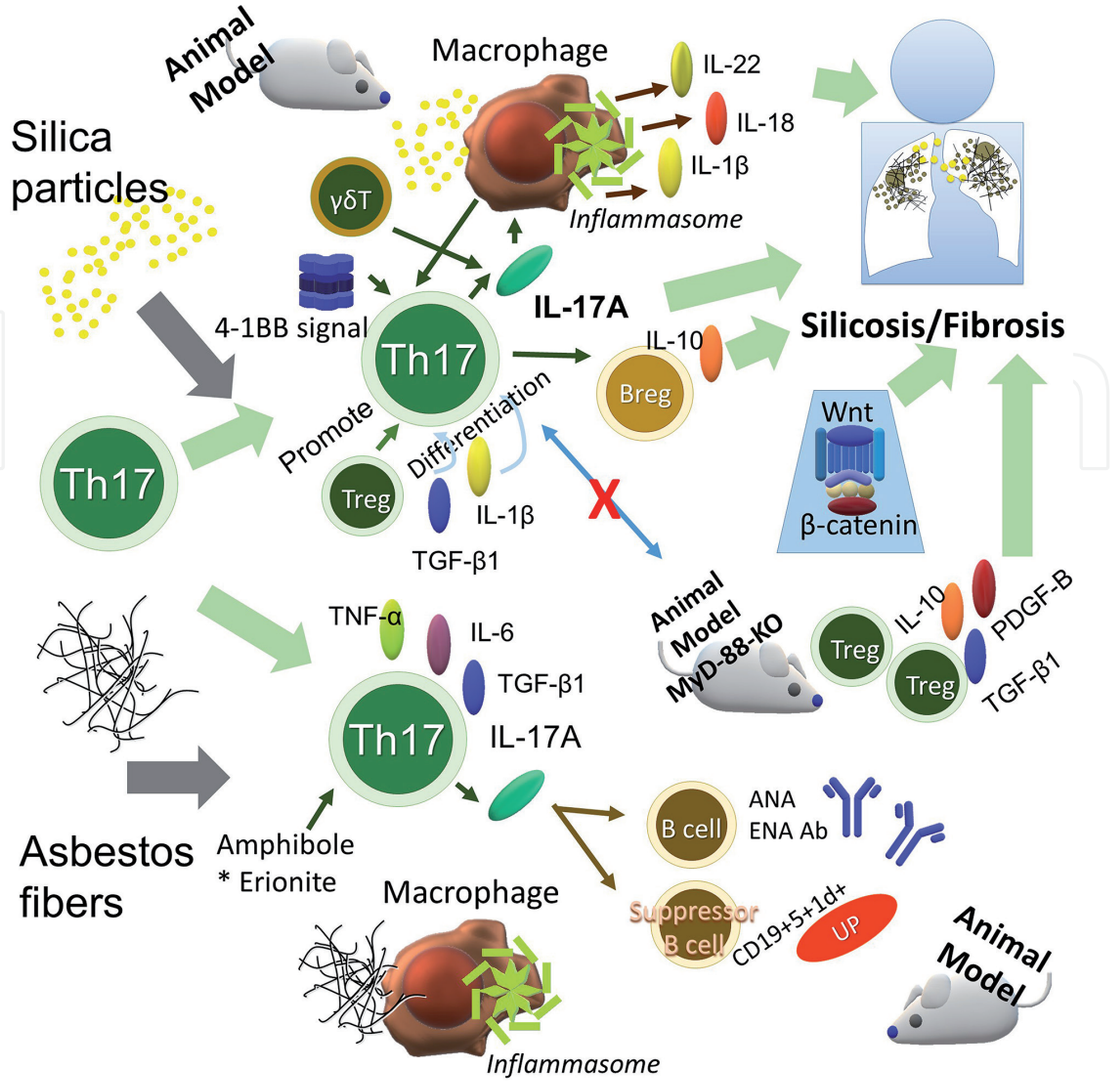

Figure 4.
Summarized effects of silica and asbestos from literatures on Th17 cell. Silica is related to the occurrence and development of lung fibrosis via Th17 cell with Treg and regulatory B cell. In addition, various molecules such as MyD-88, Wnt/β-catenin pathway, and 4-1BB signaling are also related with Th17 and silica-induced lung fibrosis. On the other hand, some reports showed amphibole asbestos and erionite affect Th17 cells to cause production of autoantibodies.

and elevation of serum concentrations of cytokines such as IL-17, I-6, TGFβ, and TNF-α [69]. Thus, they concluded that erionite and amphibole induce autoimmune dysregulation via Th17. Taken together, asbestos fibers may influence the Th17 and partially affect the occurrence of autoimmune diseases found in asbestos-exposed patients (**Figure 4**). However, the population of asbestos-induced autoimmune disease seems to be less than silica-exposed patients. Thus, further studies regarding individual factors and cellular and molecular mechanisms should be done.

5. Future overview

In this review, the immune effects of silica and asbestos are focused. Although exposure to silica particles and asbestos fibers is still an important issue in the world, recent concerns are immunotoxicity caused by exposure to nanomaterials. For example, Dhupal et al. reported that immunotoxicity of titanium dioxide nanoparticles [70]caused apoptosis via multiple Toll-like receptors and ROS-dependent mitogen-activated protein kinase (MAPK) pathway. Chen et al. reviewed immunotoxicity of silica nanoparticle [71]. They emphasized the

importance of surfaces and shapes on silica nanoparticles to cause dysfunction, cytotoxicity, and genotoxicity. Calbiati et al. studied immunotoxicity caused by silver nanoparticles [72]. They found slight stimulation of pro-inflammatory cytokine production and humoral immune responses. Although various investigations regarding immunotoxicity induced by nanomaterials have been reported, what will be induced by continuous or recurrent low-dose exposure to these materials as well as combined exposure to various materials should be considered. To establish experimental models for these views seems to be difficult, because of difficulties to assess human examples for combined exposure for various materials.

Regarding silica and asbestos focused on this review, there may be combined exposure situation. Then, although we declared silica causes dysregulation of autoimmunity and asbestos induces reduction of antitumor immunity, how exposed individual people present which types of immunotoxicities is still difficult to predict. These may be dependent on individual factors such as human leukocyte antigen (HLA) typing and other genotyping such as various single-nucleotide polymorphisms (SNPs) in the immune-related genes and microenvironmental conditions inside the individual bodies.

In addition, with investigations of exposure to various materials using animal models and cell models using human- or animal-derived various immune cells, the comprehensive strategies to evaluate multiple views regarding combined and continuous exposures should be established in the future.

6. Conclusion

In this review, the effects of silica particles and asbestos fibers on human immune cells were summarized. Both silica and asbestos effects are not only defined in the pulmonary cells but also in immune cells. Especially, since silicosis patients are often complicated with autoimmune diseases, immune effects of silica seemed to regulate to form basic status of dysregulation of immune tolerance [17, 48]. However, regarding Th17, silica exposure is involved in silica-induced lung fibrosis, contrary to the studies regarding relationship between asbestos and Th17 which had been performed on the viewpoint of autoimmune dysregulation.

In another aspect, the effects of asbestos fibers on various human immune cells such as CTL, NK cells, Tresp, and Treg indicated that asbestos exposure reduced the antitumor immunity [55]. This may involve in tumor occurrences and rapid progression of asbestos-induced cancers such as malignant mesothelioma.

The typical lung disease caused by occupational and environmental substances is pneumoconiosis, silicosis, and asbestosis. However, both particulate and fibrous substances influence the human immune system to form lung fibrosis as well as immune disorders such as alteration of autoimmunity and/or antitumor immunity. To consider these findings, it may be possible to neutralize altered immune status in silica- or asbestos-exposed people to prevent the development of lung fibrosis as well as complicated autoimmune diseases of asbestos-induced cancers by taking some agents included in foods or physiologically active substances. Further studies to investigate these possibilities may support chemoprevention for particulate fibrous material-induced health disturbances.

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Conflicts of interest

All authors declare that there are no conflicts of interest.

Author details

Naoko Kumagai-Takei[1], Suni Lee[1], Kei Yoshitome[1], Nagisa Sada[1,2], Yasumitsu Nishimura[1] and Takemi Otsuki[1]*

1 Department of Hygiene, Kawasaki Medical School, Kurashiki, Japan

2 Department of Biophysical Chemistry, Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama University, Okayama, Japan

*Address all correspondence to: takemi@med.kawasaki-m.ac.jp

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